



NDA 022275/S-007

**SUPPLEMENT APPROVAL**

Otsuka Pharmaceutical Company, Ltd.  
Attention: Craig Ostroff, PharmD.  
Senior Director, Regulatory Affairs  
1 University Square Dr., Suite 500  
Princeton, NJ 08540

Dear Dr. Ostroff:

Please refer to your Supplemental New Drug Application (sNDA) dated May 21, 2012 and received May 22, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Samsca (tolvaptan) 15 mg and 30 mg Tablets.

We acknowledge receipt of your submission dated November 12, 2012.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~striketrough text~~):

1. Under **WARNINGS AND PRECAUTIONS/Too Rapid Correction of Serum Sodium Can Cause Neurologic Sequelae** (see **BOXED WARNING**), the following text was added/~~deleted~~:

Osmotic demyelination syndrome is a risk associated with too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours). Osmotic demyelination results in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable. In controlled clinical trials in which tolvaptan was administered in titrated doses starting at 15 mg once daily, 7% of tolvaptan-treated subjects with a serum sodium <130 mEq/L had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 2% had an increase greater than 12 mEq/L at 24 hours. Approximately 1% of placebo-treated subjects with a serum sodium <130 mEq/L had a rise greater than 8 mEq/L at 8 hours and no patient had a rise greater than 12 mEq/L/24 hours. ~~None of the patients in these studies had evidence of osmotic demyelination syndrome or related neurological sequelae, but such complications have been reported following too rapid correction of serum sodium.~~ Osmotic demyelination syndrome has been reported in association with SAMSCA therapy [see Adverse Reactions (6.2)]. Patients treated with SAMSCA should be monitored to assess serum sodium concentrations and neurologic status, especially during initiation and after titration. Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction during the first 24 hours of therapy with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided.

2. Under **WARNINGS AND PRECAUTIONS/Co-administration with Hypertonic Saline**, the following text was ~~deleted~~:

~~There is no experience with concomitant use of SAMSCA and hypertonic saline. Concomitant use with hypertonic saline is not recommended.~~

3. Under **ADVERSE REACTIONS**, the following section was added:

#### **6.2 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of SAMSCA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Neurologic: Osmotic demyelination syndrome

Investigations: Hyponatremia

Removal of excess free body water increases serum osmolality and serum sodium concentrations. All patients treated with tolvaptan, especially those whose serum sodium levels become normal, should continue to be monitored to ensure serum sodium remains within normal limits. If hyponatremia is observed, management may include dose decreases or interruption of tolvaptan treatment, combined with modification of free-water intake or infusion. During clinical trials of hyponatremic patients, hyponatremia was reported as an adverse event in 0.7% of patients receiving tolvaptan vs. 0.6% of patients receiving placebo; analysis of laboratory values demonstrated an incidence of hyponatremia of 1.7% in patients receiving tolvaptan vs. 0.8% in patients receiving placebo.

4. Under **DRUG INTERACTIONS/Effects of Tolvaptan on Other Drugs**, the following text was added/~~deleted~~:

#### **Digoxin**

~~Digoxin is a P-gp substrate and SAMSCA is a P-gp inhibitor. Co-administration of SAMSCA and with digoxin results in a 1.3 fold increase in the exposure to digoxin increased digoxin by 20% and Cmax by 30%.~~

#### **Pharmacodynamic Interactions**

Tolvaptan produces a greater 24 hour urine volume/excretion rate than does furosemide or hydrochlorothiazide. Concomitant administration of tolvaptan with furosemide or hydrochlorothiazide results in a 24 hour urine volume/excretion rate that is similar to the rate after tolvaptan administration alone.

Although specific interaction studies were not performed, in clinical studies tolvaptan was used concomitantly with beta-blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium sparing diuretics. Adverse reactions of hyperkalemia were approximately 1-2% higher when tolvaptan was administered with angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium

sparing diuretics compared to administration of these medications with placebo. Serum potassium levels should be monitored during concomitant drug therapy.

As a V2 receptor antagonist, tolvaptan may interfere with the V2 agonist activity of desmopressin (dDAVP). In a male subject with mild Von Willebrand (vW) disease, intravenous infusion of dDAVP 2 hours after administration of oral tolvaptan did not produce the expected increases in vW Factor Antigen or Factor VIII activity. It is not recommended to administer SAMSCA with a V2 agonist.

5. In the Medication Guide, under **What should I tell my healthcare provider before taking Samsca?**, the following bullet was added:

- are taking desmopressin (dDAVP).

6. The revision date and version number were updated.

There are no other changes from the last approved package insert.

We have completed our review of this supplemental application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter, RN, BSN  
Regulatory Project Manager for Safety  
(301) 796-3975

Sincerely,

*{See appended electronic signature page}*

Mary Ross Southworth, PharmD.  
Deputy Director for Safety  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation 1  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R SOUTHWORTH  
11/16/2012